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10/705,644	11/10/2003	Virginia W. Cornish	59154-AZ/JPW/G	4768
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			EXAMINER	
			ROBINSON, HOPE A	
			ART UNIT	PAPER NUMBER
			1652	
			MAIL DATE	DELIVERY MODE
			11/14/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/705,644

Applicant(s)

CORNISH, VIRGINIA W.

Examiner

Hope A. Robinson

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 158-180 is/are pending in the application.
- 4a) Of the above claim(s) 173-180 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 158-172 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 November 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/24/06</u> . | 6) <input type="checkbox"/> Other: _____  |

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## **DETAILED ACTION**

### ***Application Status***

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.
2. Applicant's response to the Office Action mailed September 5, 2006 on August 6, 2007 is acknowledged.

### ***Claim Disposition***

3. Claims 1-157 have been canceled. Claims 161-180 have been added. Claims 158-180 are pending. Claims 158-172 are under examination. Claims 173-180 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim and because the claims are directed to a non-elected subject matter based on the election made from the communication mailed on August 20, 2006. These claims would have been subjected to a Restriction Requirement had they been presented in the application at the time of filing based on methods directed to a different end point with different method steps.
4. The following objections/rejections remain or are applicable:

***Drawing***

5. The drawings filed on November 24, 2006 are accepted by the examiner.

***New-Claim Objection***

6. Claim 169 is objected to because of the following informalities:

Claim 169 is objected to because the name of the organisms are not spelled out or italicized.

Correction is required.

***Claim Rejections - 35 USC 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 158-172 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for the Dex-Mtx dimerization system used to induce dimerization of LexA-GR and DHFR-B42 and the use of a lacZ reporter, does not reasonable provide enablement for the use of any screening molecule with any set of fusion proteins or any analogs of methotrexate. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of molecules comprising a methotrexate moiety and any ligand. In addition, the claimed method is directed to covalent binding of a ligand with specificity to the unknown protein target, which renders the claimed method as inoperable, because specificity would require a protein target that is known. Determination of a ligand with a known biological function that would bind to an unknown protein covalently would require undue experimentation. Further, the claimed method utilizes at least two fusion proteins and a DNA with a reporter gene, which are only described in functional terms, as no correlation is made between structure and function. The claims encompass a large genus of fusion protein

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dimerization system. It is noted that claims such as claim 161 define the fusion protein, however, the claim does not rectify the deficiency of claim 158 with respect to the genus of ligands. Due to the large quantity of experimentation necessary to generate the infinite number of analogs and ligands recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

The state of the art is unpredictable, for example, Abida et al. (ChemBioChem, 2002, vol. 3, pages 887-895) state that, "while several three-hybrid systems have been reported, little has been done to characterize these systems and understand the influence of the CID and protein-chimera structure of the transcription and infinite number of possibilities(see page 887, col. 1, paragraph 1 and page 893, last paragraph). According to Abida et al., surprisingly we find that, though both proteins are inhibited by Mtx with picomolar affinity, the transcription read-out for the two proteins differs dramatically (see page 892-893 of the reference). Abida et al. conclude that they could not explain the results obtained wherein the proteins exhibited different results, which speaks to the high level of unpredictability in the art. In addition, the claimed invention is unpredictable because the claimed method is inoperable. No indicia is provided as to the claimed analogs characteristics to be able to effect a covalent bond with a ligand that will specifically bind to a unknown protein target. The specification

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lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The specification sets forth a single working example, which does not rectify the missing information in the instant specification pertaining to the claimed genus. The nature and properties of this claim is difficult to ascertain from the example provided as one of skill in the art would have to engage in undue experimentation to practice the claimed invention commensurate in scope with the claims.

The specification does not provide support for the broad scope of the claims. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ 2d 1438, 1445 \*n.23 (Fed. Cir. 1991). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

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Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 158-172 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claim 158 is confusing. The claim in item (a) recites a molecule with a methotrexate moiety that binds dihydrofolate reductase and in item (b) recites that said molecule is introduced into a cell that expresses a fusion protein comprising dihydrofolate reductase capable of binding methotrexate, thus it is unclear if the molecule in (a) really associates with the fusion protein in (b). Further, the claim lacks antecedent basis for "wherein one of the first and second fusion proteins also comprises a transcription activator..." because there is only 1 first fusion protein and 1 second fusion protein, so the language of "one of the first fusion protein and second fusion protein" lacks clear antecedent basis. In addition, the claim is confusing as to which fusion protein (the first or the second) possesses "a transcription activator domain or DNA-binding domain" or does both have the two domains? The dependent claims hereto are also included in this rejection.



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Claims 171-172 are confusing as the claims seem to recite a Markush listing, however represents an improper Markush and there is no nexus between the items listed in the claims.

***New-Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 158-160 rejected under 35 U.S.C. 102(a) as being anticipated by Lin et al. (J. Am. Chem. Soc., 2000; Cited on IDS).

Lin et al. disclose a yeast three-hybrid assay using Dexamethasone-Methotrexate (see Figure 1 of the reference). Lin et al. disclose forming a screening molecule by covalently bonding said molecule to a substrate capable of selectively binding to and selectively forming a covalent bond with a receptor (see Figure 1 and page 4248 of the reference). Although Lin et al. does not explicitly teach a covalent bond, said bond is an inherent property based on the disclosure. In addition, Lin et al. disclose introducing the screening molecule into a cell culture comprising cells that express a first fusion protein of a DNA-binding domain fused to a target receptor domain

against which the target molecule is screened (see Figs 1 and 2; and Table 1 of the reference). Lin et al. also disclose a second fusion protein that comprises a receptor domain capable of binding to and forming a covalent bond with the screening molecule (see Fig. 1). Lin et al. disclose a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein (see Fig 1). Finally Lin et al. disclose selecting the cells and identifying the target protein. Therefore, the limitations of the claims are met by the reference.

***Response to Applicant's Arguments:***

12. Applicant's arguments have been fully considered and several rejections/objections of record have been withdrawn. Note however, that new objections have been instituted based for the reasons stated above. In addition, note that the rejection of record under 35 USC 112, first and second paragraphs remain but have been amended. Applicant's arguments pertaining to the written description are noted however are moot based on cancellation of claims and the withdrawal of the rejection. The enablement rejection remains because the claims broadly read on any ligand or molecule comprising a methotrexate moiety as stated above. Applicant's arguments have been considered in full, however are not persuasive because the instant specification is not enabled for the full scope of the claims. Applicant's arguments regarding the art are noted, however, each application is treated on its own merits and the claims are not limited to the exemplification provided in the art. Undue

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experimentation would be required for one of ordinary skill in the art to test all possible ligands with a biological function to practice the claimed invention. Note that the art rejection has been amended to a 102(a) based on applicant's comments with respect to the date of the priority document.

### ***Conclusion***

14. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Primary Examiner

*Y/A*  
*8/13/07*

HOPE ROBINSON  
PRIMARY EXAMINER